

## Renal Physiology

### Basics

2 kidneys

10-11 cm long

150g each

1 million nephrons/kidney

25% of cardiac output: RBF ~ 625ml/min/kidney

20% filtered: GFR ~ 125 ml/min (range 80-140ml/min)

Functions:

1. Excretion

a. Metabolic endproducts

Acid (organic or inorganic)

Nitrogenous waste (urea)

Nucleic acid turnover (uric acid/xanthine)

b. Drugs/Toxins

Filtration or secretion

Often same disposal as acids

2. Maintenance of fluid volume

Sodium and water regulation via RAA and in response to ADH

3. Maintenance of body fluid composition

Na<sup>+</sup>, K<sup>+</sup>, Cl<sup>-</sup>, pH, Mg<sup>+</sup>, Ca<sup>+</sup>, phosphate, water

4. Hormonal regulation

Renin

Erythropoetin

1,25 dihydrocholecalciferol

### Glomerular filtration

Passive ultrafiltration of plasma across semipermeable glomerular membrane

Determinants of GFR:

Glomerular permeability (Lp)

Glomerular surface area (S)

Pushing pressure (difference in hydrostatic pressure)

Pulling pressure (difference in oncotic pressure)

$$GFR = LpS - (\Delta \text{hydrostatic pressure} - \Delta \text{oncotic pressure})$$

(i) Glomerular permeability

Fenestrated negatively-charged (anionic) capillary endothelial cell layer with microvilli

Size and charge selective

Free filtration of water and neutral molecules less than 26 Angstroms

Some filtration of neutral/positively-charged molecules up to 60A

No filtration of highly-negative molecules (albumin) or >60A

(ii) Transglomerular hydraulic pressure

Autoregulation\* of afferent and efferent arterioles acts to maintain glomerular blood pressure at a constant 50-60mmHg

Proximal tubular hydrostatic pressure effectively zero, except when downstream obstruction

## (iii) Oncotic pressure

Constant at ~25mmHg

In normal conditions plasma proteins not filtered so Bowman's space oncotic pressure zero

Autoregulation of glomerular filtration

GFR preserved across wide range of blood pressure (80 – 180mmHg) due to 2 complimentary mechanisms:

## (i) Afferent arteriolar myogenic stretch

Laplace's law governs that a rise in pressure/increase in radius (volume) increases wall tension

Myogenic tone of afferent arteriole 'pushes' back; conversely relaxes when pressure/radius, thereby regulating flow into glomerulus

## (ii) Tubuloglomerular feedback (juxtaglomerular apparatus)

Macula densa cells in distal tubule monitor flow

Increased pressure – increased GFP – increased tubular flow

Leads to production of substances (endothelin, TXA2, AT2) from granular cells of juxtaglomerular apparatus, leading to constriction of afferent arteriole

NB. Granular cells of JGA secrete renin in predominantly in response to low tubular chloride rather than sodium. Sodium follows chloride, leading to a rise in ECF volume and blood pressure (see appendix)

Assesment of glomerular filtration

GFR cannot be measured directly – needs to be estimated. Methods comprise Plasma creatinine and other markers, mathematical formulae, and plasma clearance

(i) Plasma markers

## Creatinine

Constant production in individual

10% secreted – therefore typically overestimates GFR

Patient to patient variation based on age, sex, muscle mass and race. Low production (little old ladies) overestimates GFR; high intake (bodybuilders) underestimates GFR

Mathematical formula used to 'normalise values':

## (i) Cockcroft &amp; Gault (individuals with normal function)

$$\text{CrCl} = \frac{\{(140 - \text{age}) \times (\text{IBW in kg})\}}{[\text{PCr}(\text{mg/dL}) \times 72]} \times 0.85 \text{ (women)}$$

Does not describe a linear relationship – see graph overleaf. Also calculates creatinine clearance, not glomerular filtration rate

## (ii) MDRD (individuals with impaired renal function)

Modification of diet in renal disease (1999). Derived as a screening tool to identify patients with renal disease

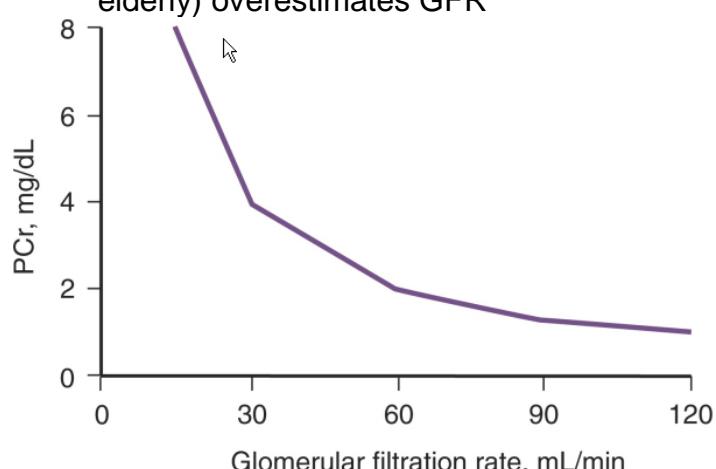
$$GFR = 186 \times (PCr)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female}) \times (1.210 \text{ if African American})$$

Calculates GFR not creatinine clearance  
 Underestimates eGFR at high values. Therefore a number of hospitals give eGFR of > 60ml/min rather than a figure for high filtration rates  
 Requires fudge factor for blacks – not calculated automatically  
 New formula CKD EPI set to supercede MDRD as better predictor across range of GFRs

Steady *reciprocal* relationship between GFR (or creatinine clearance) and serum creatinine (see below)

NB. Increased production (rhabdomyolysis, supplements) underestimates GFR

Reduced production (cirrhosis, reduced muscle mass, elderly) overestimates GFR



### Urea

Freely filtered but up to 50% reabsorption by tubule

### Cystatin C

Nucleic acid breakdown molecule. Constant production, unaffected by diet, not secreted, expensive

## (ii) Clearance

Best way of estimating GFR is by measuring clearance of a substance from plasma.

Clearance = the amount of plasma that is completely cleared of a substance per unit time.

$$Cl = [U] \times V / [P]$$

U = Urine concentration of substance

V = Volume of urine

P = Plasma concentration of substance

To be accurate the substance must:

Achieve steady state in plasma

Excreted solely by kidney

Freely filtered

Not secreted, reabsorbed or metabolised by tubule

Good example inulin, but impractical. Typically creatinine clearance, but secreted by proximal tubule, thus overestimates GFR by 10-20% at normal levels. Overestimation greater as renal function deteriorates – more creatinine secreted. Radiolabelled EDTA most accurate (DTPA can be used but slightly secreted). Typically single injection of  $^{51}\text{Cr}$ -EDTA, then measure blood levels at specified intervals 2-5 hours after injection to demonstrate decay curve.

### Tubular function

Proximal tubule	Major site of electrolyte and glucose reabsorption Secretion of organic acids/drugs and toxins
Loop of Henle	Generation of osmotic gradient for variable water reabsorption (countercurrent mechanism)
Distal tubule/ collecting duct	Additional NaCl reabsorption Hormone sensitive fine tuning Aldosterone NaCl reabsorption K <sup>+</sup> excretion ADH Water reabsorption H <sup>+</sup> excretion dependent on acid base status

### Proximal Tubule

Divided into three segments: S1/S2 concerned with reabsorption, S3 predominantly concerned with secretion

#### Reabsorption

15% Mg ++  
65% Na<sup>+</sup> \*, K<sup>+</sup>, Ca<sup>++</sup>  
80% Water, phosphate, HCO<sub>3</sub><sup>-</sup>  
100% Glucose \*\*, amino acids

\* **Na<sup>+</sup> is the only solute actively reabsorbed** via basolateral Na<sup>+</sup>/K<sup>+</sup> pump. Remainder passively reabsorbed down concentration, osmotic (water) or electrochemical gradients  
\*\* Glucose absorption threshold 200mg/dL  
Glutamine converted to ammonia throughout PCT

#### Secretion

Drugs and toxins via active organic ion (cation or anion) pumps  
Liver often converts uncharged molecules to charged ones for excretion

### Loop of Henle

Two purposes of LoH

Reabsorption of 25-30% Na<sup>+</sup>  
Generation of vertical osmotic gradient

(i) Thin descending limb

Highly water permeable (aquaporin 1 channels)  
Negligible solute transport

(ii) Thin ascending limb

Minimal water permeability  
Passive NaCl and urea diffusion down concentration gradient

(iii) Medullary thick ascending limb

Water impermeable  
25-30% Na<sup>+</sup> reabsorption

Passive transport into cell (Na<sup>+</sup>K<sup>+</sup>CLCL2 co transporter\*)

Active transport out (basolateral Na-K ATPase)

\*Targeted by loop diuretics

15% Ca<sup>++</sup>; 60% Mg<sup>++</sup> reabsorption

Passive paracellular, driven by electrochemical gradient.

Dissipation of gradient by loop diuretics inhibits Ca<sup>++</sup> and Mg<sup>++</sup> absorption

10-20% HCO<sub>3</sub><sup>-</sup> reabsorption

Minimal K<sup>+</sup> reabsorption

Recycling of K<sup>+</sup> in TALH crucial to generate electrochemical gradient

Countercurrent mechanism (300-1200 mosm/l)

NaCl and urea (50% from loop; 50% from collecting duct) make interstitium hypertonic. Water osmotically absorbed from TDLH = more concentrated urine at hairpin = more diffusion of solute = more diffusion of water, etc. Under ADH, urea and water diffuse into interstitium. Water rapidly reabsorbed by vasa recta (also aquaporins in *cortical* collecting duct) thereby preserving concentration gradient

Production of Tamm-Horsfall mucoprotein

### Distal tubule

Divided into DCT and connecting tubule

Principle cells – aldosterone dependent secretion of K<sup>+</sup>/absorption of Na<sup>+</sup>

Intercalated cells – hormone-independent absorption of K<sup>+</sup>

Distal convoluted tubule:

5-10% Na<sup>+</sup> absorption

Passive Na<sup>+</sup>K<sup>+</sup>CL2CL2 co-transport, driven by basolateral Na<sup>+</sup>/K<sup>+</sup> ATPase

Co-transporter inhibited by thiazide diuretics

Na<sup>+</sup> absorption dependent on luminal [Na<sup>+</sup>]. – frusemide increases Na<sup>+</sup> absorption by DCT (net Na<sup>+</sup> loss however)

10-15% Ca<sup>+</sup> reabsorption

Passive, independent of Na<sup>+</sup> absorption

Driven by basolateral Na<sup>+</sup>/Ca<sup>+</sup> pump (Ca<sup>+</sup> out).

Reduced intracellular Na<sup>+</sup> 2' thiazides postulated as a reason for hypocalciuric effect but exact mechanism unknown

Connecting tubule:

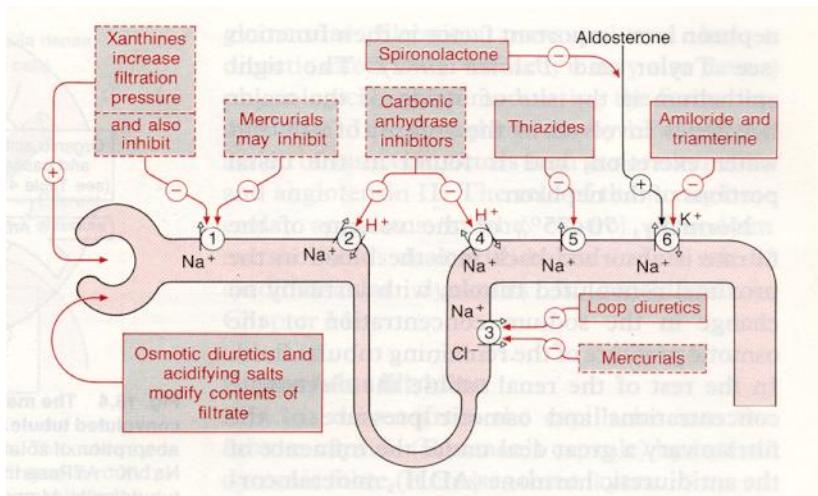
Sodium absorption and potassium loss under influence of aldosterone

K<sup>+</sup> secretion rate influenced by sodium delivery, and urine flow rate.

Tubular damage impairs potassium secretion (interstitial nephritis etc.)

	Proximal nephron	LOH	Distal nephron
Na <sup>+</sup> reabsorption*	67%	25%	8%
Water reabsorption*	65%	15%	20%
Ca <sup>++</sup> reabsorption	65%	15%	15%
Mg <sup>++</sup> reabsorption	15%	60%	10%

\* maximum values



## Diuretics

### Loop diuretics

inhibit  $\text{Na}^+ \text{K}^+ \text{Cl}^- \text{Cl}^-$  pump in TALH

Organic acids requiring secretion into PCT for effect. In renal failure more competition for secretion from accumulating toxins. Explains usage of large doses (250mg-1g) for effect in renal failure

Up to 25% increased sodium excretion

Loss of  $\text{NaCl}$ , water, K, Mg and Ca

inhibit  $\text{NaCl}$  co-transport in DCT

5-10% increased sodium excretion

Loss of  $\text{NaCl}$ , water. Loss of K by increasing sodium load to DCT.

### Thiazide diuretics

Spironolactone, amiloride, triamterine

5% increased sodium excretion

Spironolactone competes with aldosterone for intracellular mineralocorticoid receptor – inhibits  $\text{Na}^-\text{K}^+$  ATPase

Amiloride/triamterine directly blocks sodium channels

## Acid-base balance

pH 7.35 – 7.45

Tightly controlled by buffers

$\text{HCO}_3/\text{CO}_2$  principal buffer system

Lungs excrete  $\text{CO}_2$  rapidly

Kidney

Reclamation of all filtered  $\text{HCO}_3$

Excretion of  $\text{H}^+$  with generation of  $\text{HCO}_3$

Mechanisms:

glutamine into  $\text{NH}_4$  and  $\text{HCO}_3$  in PCT

$\text{H}^+$ -ATPase in DCT excretes  $\text{H}^+$  and generates  $\text{HCO}_3$  ( $\text{H}^+$  buffered by  $\text{PO}_4$  or as free acid)

## Determining appropriateness of compensation

# Boston Rules

## pH, pCO<sub>2</sub> & HCO<sub>3</sub>

### Metabolic Acidosis

- Expected CO<sub>2</sub> = 1.5 \* HCO<sub>3</sub> + 8 (+/- 2) mmHg (divide by 7.6 for kPa)
- or
- 0.2 \* HCO<sub>3</sub> + 1 kPa

### Respiratory Acidosis

- Acute: 1 mmol rise HCO<sub>3</sub> for every 10 mmHg increase in CO<sub>2</sub>
- Chronic: 4 for 10

### Respiratory Alkalosis

- Acute: 2 mmol fall in HCO<sub>3</sub> for every 10 mmHg fall in CO<sub>2</sub>
- Chronic: 5 for 10 (+/- 2) (max fall HCO<sub>3</sub> to 12-15)

### Metabolic Alkalosis

- Expected CO<sub>2</sub> = 0.7 \* HCO<sub>3</sub> + 20 (+/- 5)
- or
- Expected CO<sub>2</sub> = 0.6 \* BE + 40

In mmHg

(divide by 7.6  
for kPa)

### Anion gap and Metabolic acidosis

$$\text{Na} + \text{K} - \text{Cl} - \text{HCO}_3 \quad \begin{array}{l} \text{Normal} < 15-20^* \\ \text{High} > 15-20 \end{array}$$

\* Depends on lab measurement. Newer ion-specific techniques more accurate. New classification HIGH = 12 or above

Blood electrochemically neutral. 'Positive' anion gap because more unmeasured anions than cations. Unmeasured cations magnesium, calcium and gamma globulins. Unmeasured anions sulphates, albumin and phosphate. Where a pure loss of bicarbonate occurs, chloride released to 'bridge the gap'. In situations where new acids are produced electrochemical neutrality is maintained (salicylate plus H<sup>+</sup>), thus chloride remains unchanged

High anion gap      Lactic acidosis  
                          Ketoacidosis  
                          Salicylate poisoning

Normal anion gap    Gut losses (Vomiting, fistula, diarrhoea)  
                          Renal losses (RTA)  
                          Chloride ingestion/administration

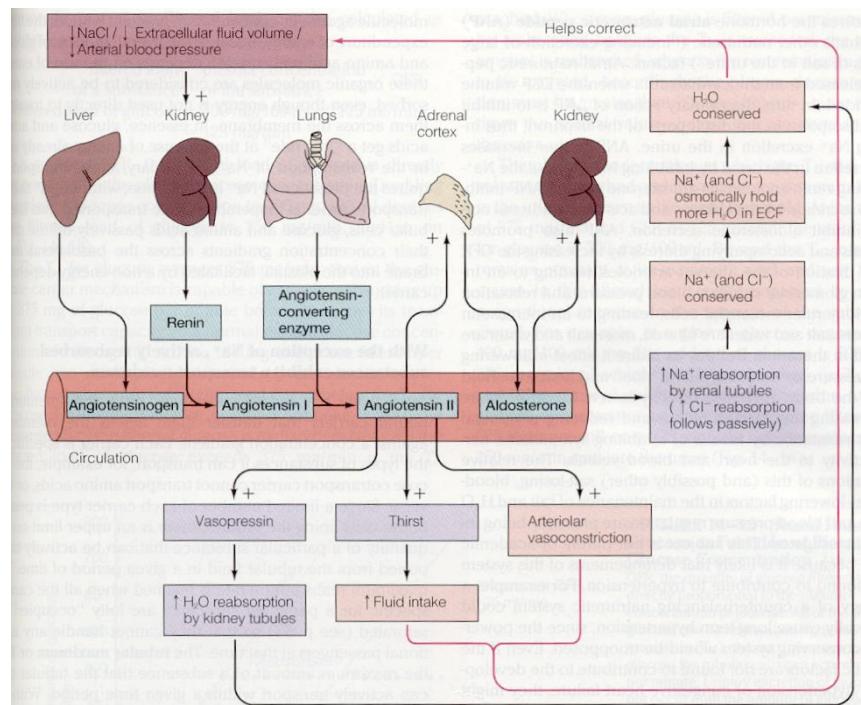
NB    Renal tubular acidosis (RTA)  
         Family of diseases characterized by failure of tubular H<sup>+</sup> secretion and urinary acidification:

Type 1	distal failure of H <sup>+</sup> secretion Diagnostic triad Hyperchloraemic metabolic acidosis High urinary pH (>5.5) Low serum HCO <sub>3</sub> Associated low sodium, hyperaldosteronism, with low potassium (and low citrate) <b>Calcium phosphate stone disease</b> – Rx with sodium bicarbonate
Type 2	Proximal failure of bicarbonate reabsorption Same triad as above, with low sodium and potassium Citrate normal - no stone disease Usually children - growth retardation and osteomalacia (Tiny Tim)
Type 3	Actually type 1
Type 4	Impaired distal H <sup>+</sup> and K <sup>+</sup> secretion. As above but with hyperkalaemia

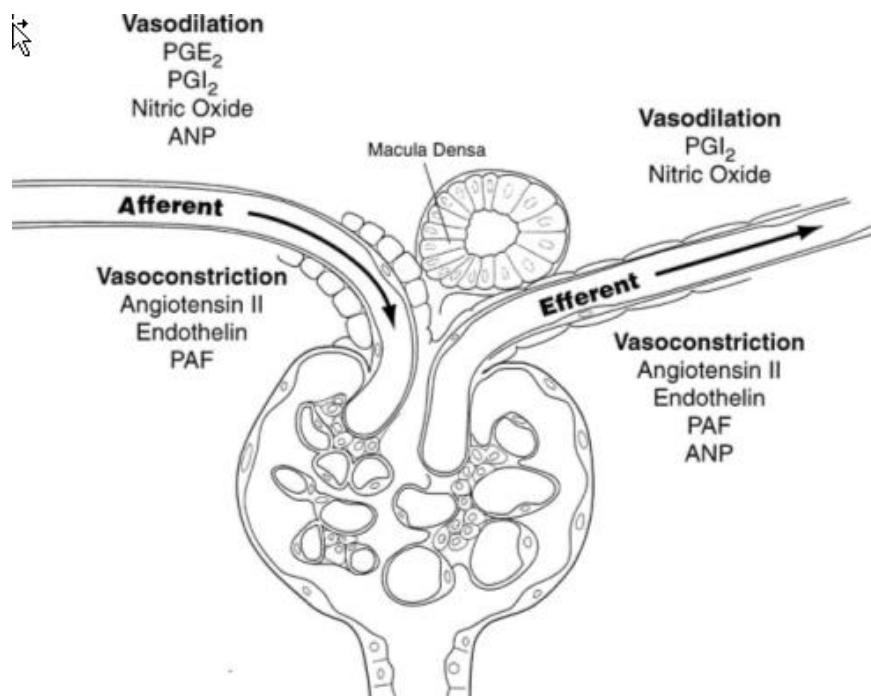
### Metabolic alkalosis

Ingested alkali normally rapidly excreted by kidney. Persistent alkalosis usually due to impairment of HCO<sub>3</sub> excretion from kidney, typically due to chloride deficiency. Replacement of Cl usually reverses alkalosis.  
 Chloride responsive = Gut losses and diuretics (90% - often with paradoxical aciduria due to aldosterone action) - low urinary Cl  
 Chloride unresponsive = mineralocorticoid excess leading to acid and potassium loss from tubule. Normal urinary Cl (>15 MEq/l)

## Homeostasis and renin-angiotensin axis



NB. Control of renin release is rate-limiting step in RAA axis



**Vasoconstrictors**

- Angiotensin 2
- Vasopressin
- Noradrenaline
- Endothelin
- Platelet activating factor

**Vasodilators**

- Nitric oxide
- Carbon monoxide
- PGE2/PGI2
- Acetylcholine
- Serotonin

ANP	Glucocorticoids
Angiotensin 2	mediates effects via AT1 receptor – efferent constriction >> afferent vasoconstriction
Endothelin	Highly potent vasoconstrictor released from endothelial cell membrane
ANP	Atrial natriuretic peptide (Cogan 1990) Released in response to increased intravascular volume Effects Increased GFR (dilatation AE and constricts EA) Inhibits juxtaglomerular apparatus (decreased renin, AT2 and aldosterone) = natriuresis Inhibits vasopressin release and effects = diuresis Prevents phase 3 (shutdown) in bilateral UO vs. unilateral UO by maintaining AE dilatation
Nitric oxide	Synthesised by endothelial NOS (eNOS) and released from endothelium
Carbon monoxide	Produced as a byproduct of heme metabolism by Heme oxygenase (HO). Exerts renoprotective effect vs ischaemia, especially in renal medulla

### Calcium homeostasis

Major source of cholecalciferol is dermal synthesis from cholesterol

Other source from diet

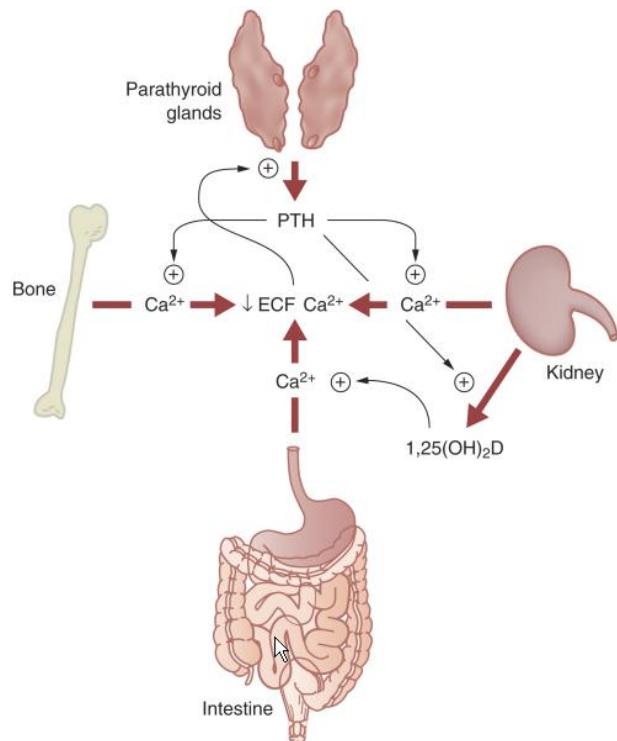
Initial 25a-hydroxylation in liver

Second 1a-hydroxylation in kidney to form 1,25 dihydroxy-cholecalciferol (calcitriol)

Acts on gut to increase calcium and phosphate reabsorption. Acts on bone to increased calcium resorption

PTH – acts on kidney to stimulate calcium reabsorption and phosphate excretion

Calcium in plasma bound to albumin (46%), complexed with citrate/phosphate (7%) or ionized/free (47%). Acidosis displaces Ca from albumin increasing free ionized calcium. Reverse in alkalosis. May not be identified as serum calcium estimation measures total calcium, not ionized forms.



Erythropoiesis

EPO produced by interstitial cells of kidney in response to low oxygen tension. HIF-1a and HIF-2a stabilised in hypoxic conditions to assemble apparatus for promoting transcription of EPO. Anaemia in renal failure simple secondary to loss of functioning interstitial cells.